Resection of subsequent pulmonary metastases from treated head and neck squamous cell carcinoma : systematic review and meta-analysis

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ORIGINAL ARTICLE

Resection of subsequent pulmonary metastases from treated head and neck squamous cell carcinoma: systematic review and meta-analysis

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Background: Pulmonary metastasectomy involves the surgical removal of pulmonary nodules. It is a recognised therapeutic modality for the treatment of metastatic disease. There is no consensus as to the role of pulmonary metastasectomy in squamous cell carcinoma of the head and neck. The objective of this study was to determine whether, in selected patients, resection of subsequent pulmonary metastases prolongs survival in patients already treated for head and neck squamous cell carcinoma and to identify independent risk factors that influence 5-year survival of patients undergoing pulmonary metastasectomy.
Methods: A systematic review of English and non-English articles using MEDLINE (1950-present), EMBASE (1980-present), NHS evidence and Cochrane databases. Search terms included but were not limited to: squamous cell carcinoma, pulmonary metastasectomy or resection, head and neck cancer, malignancy or tumour. Studies examining outcomes for patients with head and neck squamous cell carcinoma who underwent pulmonary metastasectomy for metachronous pulmonary metastases were included. Independent data extraction of articles by two trained researchers using predefined data fields was performed.
Results: Thirteen of 47 studies (all retrospective) fulfilled eligibility criteria, with a total of 403 patients. In total, 11 papers reported 5-year survival rates (Kaplan–Meier) in 387 patients with head and neck squamous cell carcinoma following pulmonary metastasectomy. Meta-analysis of survival data showed an overall absolute 5-year survival rate of 29.1% for patients undergoing pulmonary metastasectomy for metachronous metastases from head and neck squamous cell carcinoma. Two papers reported significantly worse 5-year survival rates in patients with oral head and neck squamous cell carcinoma compared with other sites (9.2% *versus* 32.4%, $P < 0.001$ and 15.4% *versus* 45.2%, $P = 0.01$). Two papers reported that the presence of cervical lymph node metastases at diagnosis of the primary tumour significantly worsened 5-year survival rates following pulmonary metastasectomy (13.8% (N+) *versus* 32% (N0) $P = 0.01$ and 24% (N+) *versus* 60% (N0) $P = 0.025$). Other significant poor prognostic factors included incomplete pulmonary resection and the presence of multiple pulmonary nodules.
Conclusions: This systematic review provides level 2a evidence of the effectiveness of pulmonary metastasectomy for metachronous pulmonary metastases from head and neck squamous carcinoma, which may offer prolonged survival for selected patients. Poor prognostic factors for pulmonary metastasectomy in this cohort of patients include the presence of lymph node metastasis at the diagnosis of the original tumour, squamous cell carcinoma of the oral cavity, incomplete pulmonary resection and the presence of multiple pulmonary nodules.

Reports of the incidence pulmonary metastases in patients with squamous cell carcinoma of the head and neck range from 1.6% to 40%.[1,2] The lung is the most common site of distant metastasis in head and neck squamous cell carcinoma and accounts for 66% of all sites.[3] When distant metastases develop, the likelihood of long-term survival becomes very low, and the disease is usually considered incurable.[4]

Pulmonary metastasectomy involves the surgical removal of metastatic nodules in the lung and is a recognised treatment modality in a number of different cancers including colorectal cancers, sarcoma, melanoma and renal cell carcinoma.[5] In general, a consensus has been reached regarding eligibility for pulmonary metastasectomy: the primary disease must be controlled; there should be no other distant disease; complete resection of the pulmonary disease

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is possible with adequate pulmonary reserve; and there are no other effective medical therapies.[5] Pastorino *et al.* retrospectively reviewed 5206 cases of pulmonary metastasectomies for a number of different primary cancers from the International Registry of Lung Metastases. They found that the most important determinant of survival was resectability. The overall 5-year survival for patients who underwent complete resection was 36% compared to 13% for patients who underwent incomplete resection.[6]

To date, there are no randomised controlled trials of outcomes following pulmonary metastasectomy in head and neck squamous cell carcinoma, compared to either medical therapy or observation.[5] This is not surprising, considering the dismal prognosis for metastatic head and neck squamous cell carcinoma, it would be difficult to ethically justify randomising a patient to non-surgical management over pulmonary metastasectomy as non-surgical management is invariably palliative, particularly if the patient was fit enough to undergo surgery. Most retrospective reviews compare the outcomes to historical data of the efficacy of chemotherapy alone when used in a palliative setting. The 5-year survival rate for chemotherapy for this indication is <5%.

Objectives

The aim of this study was to examine the survival rates of patients with metastatic head and neck squamous cell carcinoma who underwent pulmonary metastasectomy. We undertook a systematic review of the literature that assessed survival rates following this procedure in patients with metastatic head and neck squamous cell carcinoma and compared these with historical data for controls (patients undergoing no treatment or non-surgical treatment).

Methods

Definitions

The histological appearance of pulmonary metastasis following head and neck squamous cell carcinoma is similar to the histological appearance of a second primary lung cancer (SPLC). Differentiation between the two often depends on clinical criteria including head and neck squamous cell carcinoma tumour stage, disease-free interval, number and site of the pulmonary lesions as well as radiologic appearance.[1] There is, therefore, a risk that some tumours clinically diagnosed as metastatic may in fact be second primaries, which potentially may have better outcomes. Furthermore, patients with head and neck squamous cell carcinoma are at increased risk of a second lung primary; the relative risk of a second lung primary in this context is three to six times that of the normal population.[1] For the purposes of this study, a pulmonary metastasis following treatment for head and neck squamous cell carcinoma is accepted as such if reported as metastasis by clinical and histological criteria.

Ethical considerations

This article represents a systematic retrospective review of previously published articles, and no patient identifiable details are included.

Protocol and information sources

Methods of analysis and inclusion criteria were specified in advance and documented in a protocol. Studies were identified by searching electronic databases, and scanning reference lists of articles. No limits were applied for language or date of publication. The search strategy was applied to Medline (1966-present), Embase (1980-present), NHS evidence and Cochrane databases. We used the following search terms to search all databases: 'pulmonary' or 'thoracic' or 'lung' AND 'metastasectomy' or 'resection' AND 'cancer' or 'carcinoma' or 'squamous cell carcinoma' or 'malignancy' or 'tumour' or 'tumor' AND 'head and neck' or 'larynx' or 'pharynx' or 'oropharynx' or 'hypopharynx' or 'nasopharynx' or 'oral' or 'tonsillar' or 'tongue'. The full electronic search strategy is presented in Appendix 1.

Selection of articles

Eligibility assessment was performed independently in an unbiased standardised manner by one reviewer. Abstracts were screened using *a priori* criteria. The full articles of the selected abstracts were then reviewed in detail for eligibility by two trained reviewers. Eligibility criteria were set before the start of the study. These were as follows: all patients had locoregional control of the primary tumour at the time of pulmonary metastasectomy, none had distant metastases elsewhere, and all reported survival outcome data on pulmonary metastasis from head and neck squamous cell carcinoma, confirmed following histological examination.

Inclusion criteria

Randomised control trials, prospective case series or case–control studies examining outcomes following pulmonary metastasectomy in patients with pulmonary metastases from head and neck squamous cell carcinoma were included, if available. All surgical approaches to pulmonary metastasectomy and both incomplete and complete resection were included, as well as multiple or bilateral pulmonary nodules.

No language or publication date restrictions were imposed. Participants with metastatic pulmonary disease at the initial diagnosis of head and neck squamous cell carcinoma were excluded. Participants with additional non-pulmonary metastases, uncontrolled primary sites and nodules found not to be consistent with pulmonary metastases from head and neck squamous cell carcinoma were also excluded.

Data collection

We developed a data extraction pro forma and carried out a pilot test on 10 randomly selected included studies and refined it accordingly. Data extraction was performed independently and separately by two trained reviewers. Disagreements were resolved by discussion between the two reviewers, and then by discussion with the senior author. Data were extracted from each included study on: characteristics of study patients (including age at pulmonary metastasectomy, gender, histology, site and stage of primary tumour, treatment given for primary tumour); details of the metastatic pulmonary lesion [including number, size and site of nodules and disease-free interval (disease-free interval)]; details of the pulmonary metastasectomy procedure (including the operation performed, the approach, whether the lesion was resectable and details of any additional treatment); and outcome measures (including 1-, 3-, and 5-year survival rates).

Quality of studies

To ascertain the quality of eligible studies, the reviewers evaluated the articles according to the following criteria: is the study based on a representative sample selected from a relevant population; do the authors explicitly state the criteria for inclusion; was follow-up long enough to reach conclusions regarding survival rates; were patients matched to controls; were baseline characteristics reported on for head and neck squamous cell carcinoma patients; and was data provided for the nature and number of pulmonary nodules resected.

Outcome measures

The primary outcome measure was the absolute 5-year survival rate of patients with squamous cell carcinoma of the head and neck following pulmonary metastasectomy compared with historical controls not undergoing surgery.

Statistical analysis

We obtained an estimate of the between-study variance with a random-effects meta-analysis. The square root of this number is the estimated standard deviation of underlying effects across studies. As we had relative measures of effect, the confidence intervals were centred on the natural logarithm of the pooled estimate and the limits exponentiated to obtain an interval on the ratio scale. We tested for heterogeneity of the data using the Cochran's Q test and the I^2 statistic.

Results

Study selection

The search of MEDLINE, EMBASE, NHS evidence and Cochrane databases provided a total of 42 citations. A further five papers were identified by checking the references of relevant papers. After reviewing the abstracts of the papers, 27 of these 47 papers were excluded as they did not meet the *a priori* selection criteria. The full text of the remaining 20 papers was examined in detail. Thirteen papers met the inclusion criteria, published between 1986 and 2011, and were included in the review (see Fig. 1). The reasons for the rejection of the seven others were as follows: the lung tumour was not confirmed as metastasis from head and neck squamous cell carcinoma (two articles); they described non-head and neck squamous cell carcinoma primary tumours (two articles); and they were inappropriate study types in another three articles (two review articles, one letter). Of the 13 studies, six also included patients with primary tumours other than squamous cell carcinoma; these patients were excluded from our analysis.

Participants

The studies included 403 patients. Only four studies reported the mean age of the patients with head and neck squamous cell carcinoma undergoing pulmonary metastasectomy. This is partially due to the fact that a proportion of the studies also included patients with non-squamous cell carcinoma of the head and neck; in these, data were reported for the whole group of patients rather than the subgroup of patients with head and neck squamous cell carcinoma. In studies reporting age, the mean age of patients was 60 years (range of 21–81 years). Ten studies with 320 patients reported the site of the primary tumour. The most common site was the oral cavity, including the oral tongue (96 patients, 30%), followed by the larynx (88 patients, 27.5%), the hypopharynx (42 patients, 13%) and the oropharynx, including tonsil and base of tongue (25 patients, 7.8%).

Study characteristics

All studies were retrospective reviews of either patient case notes or of national databases. One study also included a matched-pair analysis of patients operated on *versus* patients

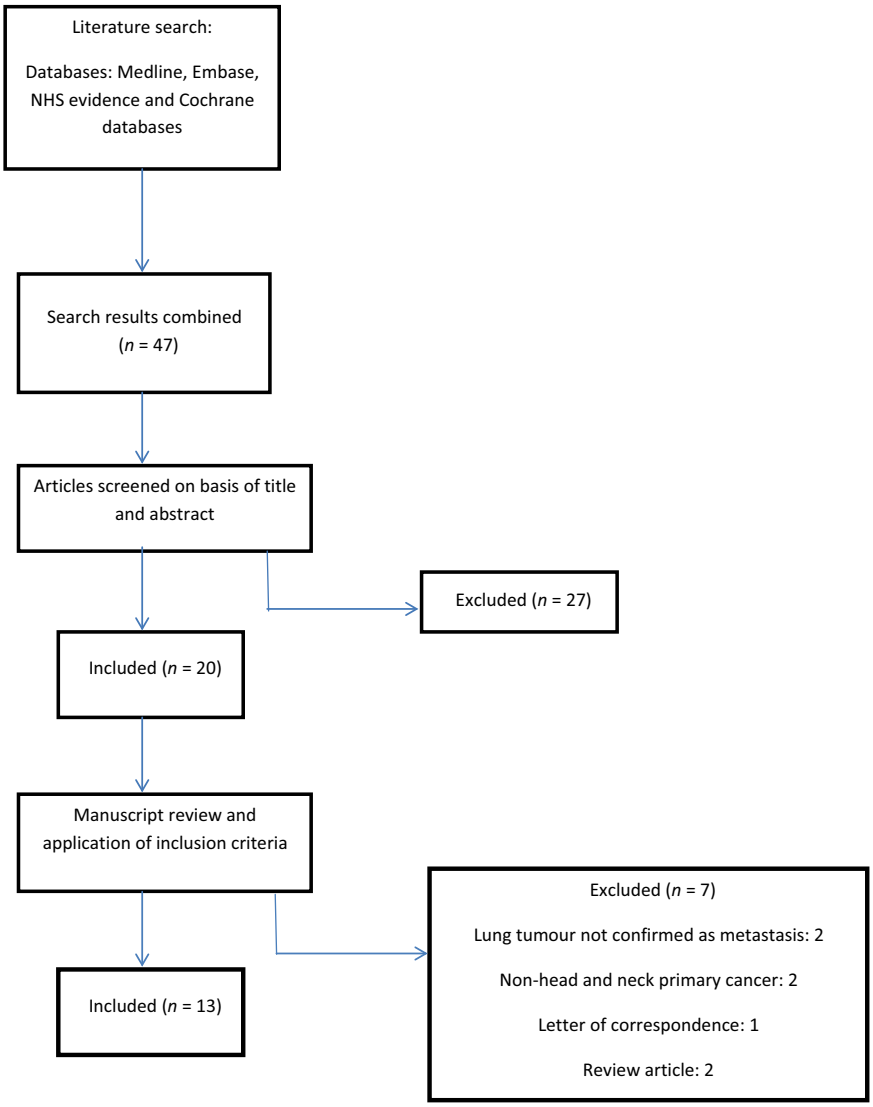

Fig. 1. Flow diagram of study selection.

not operated on. Further details of the studies are included in Table 1. The quality of the studies was mainly moderate/poor, and there was considerable risk of bias within studies (see Table 2).

Interventions and outcomes

Complete data for disease-free interval, defined as the duration from initial treatment of the primary tumour to diagnosis of the pulmonary metastasis, were only reported in four studies. These reported median disease-free intervals of 12, 16, 21 and 36 months. Eight of the studies reported the number of nodules resected. Of 286 patients, 197 (69%) had a single nodule resected; the remaining 89 (31%) had multiple nodules (up to a maximum of six) resected. Six studies (227 patients) reported the type of operation performed to resect the pulmonary nodule. The most common operation was a lobectomy, performed in 116 (51%) patients (see Table 3). Five studies stated whether the resection of the pulmonary metastasis was complete or incomplete. Of these 216 patients, 159 (74%) were reported to have had complete resection of their disease.

Overall survival following pulmonary metastasectomy for metastatic head and neck squamous cell carcinoma

Absolute 5-year survival rates, extrapolated from Kaplan–Meier survival rates, with 95% confidence intervals, following pulmonary metastasectomy in patients with squamous cell carcinoma of the head and neck are presented in Table 4.

Data were available for 5-year survival rates from 11 of the 13 studies, a total of 387 patients. Meta-analysis of survival

Table 1. Summary of included studies evaluating outcomes following pulmonary metastasectomy (PM) for squamous cell carcinoma of the head and neck

Source	No. of participants	Mean age at PM (if reported)	Age range in years at PM (if reported)	Type of study	Setting	Site of primary tumour	Outcomes
Geurts (2009)[1]	8	61	37–73	Retrospective case note review	National database, the Netherlands	Larynx: 4 Hypopharynx: 1 Oropharynx: 1 Oral: 2	5-year Kaplan–Meier survival rates
Nibu (1997)[2]	32	NR	NR	Retrospective case note review	Single Hospital, Japan	Larynx: 5 Hypopharynx: 9 Oropharynx: 1 Oral: 13 Nasopharynx: 1 Sinonasal: 2 Other: 1	5-year Kaplan–Meier survival rates
Mochizuki (2011)[7]	23	NR	28–72	Retrospective case note review	Two hospitals, Japan	Oral (tongue)	1-,2-, and 3- year Kaplan–Meier survival rates
Haro (2010)[8]	15	NR	NR	Retrospective case note review	Single hospital, Japan	Larynx: 4 Pharynx: 3 Oral: 5 Sinonasal: 3	5-year Kaplan–Meier survival rates
Chen (2008)[9]	10	NR	NR	Retrospective case note review	Single hospital, Japan	Larynx: 1 Pharynx: 3 Oral: 6	1-,2-,3- and 5-year Kaplan–Meier survival rates
Daiko (2010)[10]	27	NR	NR	Retrospective case note review	Single hospital, Japan	Larynx: 6 Hypopharynx: 8 Oropharynx: 3 Oral: 7 Nasopharynx: 3	1- and 3-year Kaplan–Meier survival rates
Shiono (2009)[11]	114	63	26–81	Retrospective database review	National database, Japan	Larynx: 32 Hypopharynx:24 Oropharynx: 7 Oral: 27 Nasopharynx: 3 Sinonasal: 9 Salivary: 4 Other: 8	5-year Kaplan–Meier survival rates
Winter (2008)[12]	55	NR	NR	Matched pair-analysis of patients operated/ not operated	Single hospital, Germany	NR	5-year Kaplan–Meier survival rates
Mazer (1988)[13]	44	61.5	21–78	Retrospective case note review	Single hospital, USA	Larynx: 11 Pharynx: 11 Tongue: 6 Tonsil: 7 Oral: 4 Other: 5	5-year Kaplan–Meier survival rates

Table 1. continued

Source	No. of participants	Mean age at PM (if reported)	Age range in years at PM (if reported)	Type of study	Setting	Site of primary tumour	Outcomes
Rendina (1986)[14]	6	56.2	50–61	Retrospective case note review	Single hospital, Italy	Larynx: 6	Survival time in months
Wedman (1996)[15]	10	NR	NR	Retrospective case note review	Single hospital, the Netherlands	NR	NR
Liu (1999)[16]	41	NR	NR	Retrospective case-note review	Single Hospital, USA	Larynx: 19 Pharynx: 13 Oral: 9	5-year Kaplan–Meier survival rates
Finley (1992)[17]	18	NR	NR	Retrospective case note review	Single Hospital, USA	NR	5-year Kaplan–Meier survival rates

NR, not reported.

data showed an overall absolute 5-year survival rate of 29.1% (24.1–35.3, 95% confidence interval) for patients undergoing pulmonary metastasectomy for metastasis from squamous cell carcinoma of the head and neck. There was no evidence of heterogeneity in this data (I^2 = 0%, P = 0.462, d.f. = 10).

Prognostic factors

Prognostic factors for survival following pulmonary metastasectomy were also examined, including the site of the primary tumour, disease-free interval, the completeness of resection, age of the patient and whether there were metastatic cervical lymph nodes present at the initial diagnosis.

Site of the primary tumour. Two authors examined whether the site of the primary tumour affected prognosis. Shiono showed a significant difference between the 5-year survival of patients with oral squamous cell carcinoma and non-oral squamous cell carcinoma following pulmonary metastasectomy (9.2% and 32.4%, respectively, risk ratio 3.67, $P < 0.001$).[11] This was supported by findings from Nibu *et al.*[2] who also showed significantly worse 5-year survival in patients with oral squamous cell carcinoma compared to non-oral squamous cell carcinoma (15.4% and 45.2%, respectively, P = 0.01). Mochizuki *et al.*[7] examined exclusively oral tongue squamous cell carcinoma and also found lower 5-year survival rates than other studies which included a number of difference sites (see Table 4).

Primary cervical lymph node metastases. Shiono *et al.* showed the presence of cervical lymph node metastases at the diagnosis of the primary tumour was a significant negative prognostic factor. Patients with cervical lymph node metastasis at initial diagnosis were found to have a 5-year survival of 13.8% compared to survival of 32% (P = 0.01) in patients with negative lymph nodes.[11] This is supported by Mazer *et al.*[13] who found increased 5-year survival rates in patients with no lymph node metastases (60% *versus* 24%, P = 0.025).

Disease-free interval. Shiono *et al.* found significantly worse prognosis when disease-free interval was <24 months. Patients with disease-free interval <24 months had a 5-year survival of 21% compared to patients with a disease-free interval of more than 24 months who had a 5-year survival of 40% (P = 0.044).[11] This was supported by findings from Mazer *et al.*[13] who also showed a longer disease-free interval equated with improved survival; patients with disease-free interval 12–24 months had greater 5-year survival than patients with disease-free interval of <12 months (83% and 20%, respectively, $P < 0.005$). Nibu *et al.*[2] also showed that a longer disease-free interval (13–24 months) correlated with improved survival compared to a shorter disease-free interval (0–12 months), although this was not statistically significant (41.7% and 23.9% respectively, P = 0.16). Finley *et al.*[17] observed patients with a disease-free interval of <1 year had a 5-year survival rate of 0%, compared with a rate of 43% in patients with a disease-free interval between 1 and 2 years.

Completeness of resection. Shiono *et al.* showed that incomplete resection of the pulmonary nodule/s affected survival. Patients with incomplete resection (n = 12) had a significantly worse 5-year survival than patients with complete

Table 2. Quality assessment of included studies

Author	Relevant population?	Explicit criteria for inclusion?	Was follow-up long enough?	Were patients matched to controls?	Were data provided regarding the nature and number of nodules resected?
Geurts[1]	Yes	Yes	Yes, although one patient lost to follow-up after 30 months	No	Yes
Nibu[2]	Yes	Yes	Yes – follow-up for at least 3 years following PM or until death	No	Yes
Mochizuki[7]	Yes but oral tongue SCC only	Yes	Yes, one patient lost to follow-up at 24 months, all the rest until death	No	Yes
Haro[8]	Yes	Yes	Not stated	No	No
Chen[9]	Yes	Yes	Yes	No	No
Daiko[10]	Yes	Yes	No – median follow-up 21 months	No	No
Shiono[11]	Yes	Yes	Yes	No	Yes
Winter[12]	Yes	Yes	No – mean follow-up 29.4 months, patients alive at last follow-up	Yes – matched paired analysis of patients operated/not operated on	No
Mazer[13]	Yes	Yes	No	No	Yes
Rendina[14]	Yes but laryngeal SCC only	Yes	No – follow-up only to a maximum of 55 months	No	Yes
Wedman[15]	Yes	Yes	Not stated	No	No
Liu[16]	Yes	Yes	No – follow-up to a median of 38 months, patients alive at last follow up	No	Yes
Finley[17]	Yes	No	No – all patients followed up until death, apart from seven who were followed up to a median of 24 months	No	Yes

resection ($n = 102$) (25% and 26.7%, respectively, risk ratio 2.47, $P = 0.037$).[11]

Number of pulmonary metastases. Finley *et al.* demonstrated that patients with multiple pulmonary nodules had a poorer prognosis than those with a single nodule. Patients with multiple metastases had a 0% 5-year survival compared with a 50% survival in patients with a single metastasis ($P = 0.02$).[17] However, Shiono showed no survival advantage in patients with a solitary metastasis compared to multiple metastases (26% *versus* 27.3% 5-year survival, $P = 0.646$).[11]

Age, gender and smoking history. Nibu *et al.* demonstrated that younger patients at the time of pulmonary metastasectomy had an improved outcome compared to older patients. Patients between the ages of 31 and 55 years had a 5-year survival rate of 48.6% compared to patients between the age of 56 and 73 years, who had a 5-year survival rate of 10.3% ($P = 0.07$).[2] In the study conducted by Shiono *et al.*,[11] men had worse 5-year survival than women (22.9% and 41.3%), although this difference was not significant ($P = 0.355$). None of the studies examined smoking history as a prognostic factor.

Discussion

We systematically reviewed and performed a meta-analysis on retrospective case series examining absolute survival rates following pulmonary metastasectomy and found an absolute 5-year survival rate of 29.1% on meta-analysis. Compared to published outcomes of alternative treatments for pulmonary metastases from head and neck squamous cell carcinoma, pulmonary metastasectomy appears to offer a survival advantage. To date, there are no randomised controlled trials that examine the efficacy of pulmonary

Table 3. Type of procedure, number of nodules resected and completeness of resection

Author	Total number of patients	Type of procedure					Number of nodules resected		Resection	
		Pneumonectomy	Bilobectomy	Lobectomy	Wedge resection	Segmental resection	Single	Multiple	Complete	Incomplete
Geurts[1]	8	0	0	3	5	0	4	4	NR	NR
Nibu[2]	32	2	4	26	0	0	26	6	4	28
Mochizuki[7]	23	5	3	13	2	0	20	3	16	7
Haro[8]	15	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chen[9]	10	NR	NR	NR	NR	NR	NR	NR	NR	NR
Daiko[10]	27	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shiono[11]	114	5	0	62	37	10	84	30	102	12
Winter[12]	55	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mazer[13]	44	1	0	9	34	0	28	16	NR	NR
Rendina[14]	6	0	2	3	2*	0	5	1	6	0
Wedman[15]	10	NR	NR	NR	NR	NR	NR	NR	NR	NR
Liu[16]	41	NR	NR	NR	NR	NR	20	21	31	10
Finley[17]	18	NR	NR	NR	NR	NR	10	8	NR	NR

NR, not reported.
*One patient underwent lobectomy and wedge resection in the same procedure.

Table 4. Absolute 5-year survival rates following pulmonary metastasectomy in patients with HNSCC

Author	Estimated absolute 5-year survival rate	Number of patients in study	Weights	95% confidence interval	
				Lower	Upper
Geurts[1]	0.25	8	2	0.06	1.00
Nibu[2]	0.31	32	10	0.17	0.58
Mochizuki[7]	0.04	23	1	0.01	0.31
Haro[8]	0.27	15	4	0.10	0.71
Chen[9]	0.40	10	4	0.15	1.07
Daiko[10]	0.22	27	6	0.10	0.49
Shiono[11]	0.26	114	30	0.18	0.38
Winter[12]	0.20	55	11	0.11	0.36
Mazer[13]	0.43	44	19	0.28	0.68
Liu[16]	0.34	41	14	0.20	0.58
Finley[17]	0.28	18	5	0.12	0.67
Combined*	0.291[†]	387	–	0.241	0.353

*Two studies not included where data are not available. Decimal values round to the nearest number.
[†]Cochrans *Q* test for heterogeneity: Q = 9.761 on 10 degrees of freedom ($P = 0.462$).

metastasectomy. In all the studies we examined, patients were selected for pulmonary metastasectomy based on their fitness to survive major surgery and were therefore likely to be fitter generally than patients not offered surgery.

Historically, the development of pulmonary metastases in head and neck squamous cell carcinoma has heralded a very poor prognosis, with treatment usually directed towards palliation. Lefor *et al.*[18] reviewed 15 patients with pulmonary metastases from head and neck cancers (of mixed histology) who did not undergo pulmonary metastasectomy and found 1-year survival to be only 7%. Dennington *et al.*[19] found only a 10% 2-year survival rate after the discovery of pulmonary metastases in patients with head and neck squamous cell carcinoma. Wedman *et al.*[15] surveyed a group of 117 patients with pulmonary metastases from cancer of the head and neck who did not undergo pulmonary metastasectomy and found them to have a 5-year survival rate of only 4%, although they did not separately analyse patients with squamous cell carcinoma. Winter *et al.* performed a matched-pair analysis based on age, sex and histology of the primary tumour, for survival of patients operated on and those not operated on. Although their study

included cancers of mixed histology, they did show a significant survival advantage in patients who underwent pulmonary metastasectomy; patients undergoing surgery had a median survival of 19.4 months compared to 5 months in patients not undergoing surgery ($P < 0.001$).[12]

Our systematic review has defined a number of variables that suggest an improved prognosis following pulmonary metastasectomy. These include younger age, female gender, non-oral squamous cell carcinoma, no cervical lymph node metastases on diagnosis of the primary tumour, a long disease-free interval and complete resection of the pulmonary metastasis. Squamous cell carcinoma of the oral cavity predicts poorer outcome than other sites, although the reasons for this are not clear. It is likely that the biological aggressiveness of oral squamous cell carcinoma is responsible for this, rather than any other factor. It is also not clear why cervical lymph node metastasis at initial diagnosis should affect survival following pulmonary metastasectomy, but may also indicate aggressiveness of the initial tumour. The disease-free interval is possibly another indicator of tumour aggressiveness.

Limitations

One major flaw of many of the studies is that it is often difficult to distinguish between a metastatic pulmonary nodule and a SPLC as discussed previously. Prior to 2005, there was no reliable histological method for differentiation between a head and neck squamous cell carcinoma metastasis and a SPLC. Diagnosis of metastasis rather than a SPLC is made by examining a number of criteria including histological features, stage of the head and neck squamous cell carcinoma, site and number of pulmonary lesions, disease-free interval and radiologic appearance. Many patients with head and neck squamous cell carcinoma have a strong smoking history, which is also a risk factor for a SPLC. Loss of heterozygosity analysis is a relatively new molecular method of distinguishing between the two. A report by Geurts *et al.*[20] on loss of heterozygosity analysis revealed that 18 of 44 cases of squamous cell lung lesions which had been clinically interpreted as metastases from head and neck cancers, were considered to be SPLC. It is possible that some of the data presented relate to SPLC rather than head and neck squamous cell carcinoma metastases. However, in terms of prognosis following pulmonary resection, differentiation between metastasis and a SPLC may not carry any significance. Geurts *et al.*[1] studied the survival of patients following resection of molecularly defined SPLC and compared this to survival of patients following resection of molecularly defined head and neck squamous cell carcinoma metastasis and found no difference in survival between the two. It would therefore seem that the more important issue is whether they are deemed resectable rather than whether they are metastasis or a SPLC.

Our study has several limitations, however. The meta-analysis reported here combines data across these studies to estimate survival rates with more precision than is possible in a single study, and there was no heterogeneity in our data. The quality of the studies varied, and no study directly compared outcomes following pulmonary metastasectomy with patients not undergoing surgery in this specific population of patients with head and neck squamous cell carcinoma. There was a large variation in the publication year of the studies and treatment protocols, follow-up and surgical technique for both the primary tumour and pulmonary metastasectomy may have changed over time.

Clinical implications

There is now recognition that HPV-positive head and neck squamous cell carcinoma behaves in distinct ways compared to HPV-negative head and neck squamous cell carcinoma Leemans *et al.*[21]. Although HPV-positive head and neck squamous cell carcinoma tumours are less likely to recur locally, the rate of distant metastasis is similar to that of HPV-negative head and neck squamous cell carcinoma Huang *et al.*[22] Huang *et al.* (2013) compared the natural course of distant metastases following treatment for HPV-positive oropharyngeal carcinoma and compared this to a cohort of patients with metastasis from HPV-negative oropharyngeal carcinoma. Whilst the rate of distant metastasis was similar between the two groups, the survival rate after distant metastasis was higher in the HPV-positive group compared to the HPV-negative group (11% *versus* 4% at 2 years, $P = 0.02$). However, the fact that these patients were younger and less likely to smoke, most likely influenced their rate of survival. As yet, there is no evidence to suggest that HPV-positive metastases should be treated any differently from non-HPV metastases with regard to pulmonary metastasectomy.

Our systematic review and meta-analysis demonstrate that certain carefully selected patients with lung metastasis following treatment for squamous cell carcinoma of the head and neck may benefit from pulmonary metastasectomy. It is important to appropriately identify those patients who might benefit from more radical treatment, including pulmonary metastasectomy.

Research implications

To date, there is little objective evidence regarding the efficacy of pulmonary metastasectomy compared to non-surgical treatment for metastatic head and neck squamous cell carcinoma. This review consists of retrospective cohorts

of patients treated between 1986 and 2011. With the changing epidemiology of head and neck squamous cell carcinoma, particularly the increase in HPV-positive tumours, there is a need for randomised controlled trials with tighter inclusion and exclusion criteria, possibly with a molecular diagnosis of metastasis to rule out SPLC and stratification by HPV status and primary tumour.

Conclusion

This systematic review and meta-analysis provide evidence of the possible efficacy of metastasectomy for pulmonary metastasis from squamous cell cancers of the head and neck. Good prognostic factors include younger patients, female gender with non-oral squamous cell carcinoma, long disease-free interval, a single pulmonary nodule, complete resection of the pulmonary metastasis and no nodal metastasis at presentation. It shows evidence for a trend in increased survival in patients undergoing pulmonary metastasectomy compared to those who are not operated on. Further research in this area is needed, preferably in the form of randomised controlled trials.

Keypoints

- Pulmonary metastasectomy appears to offer an appreciable survival advantage in carefully selected patients.
- Good prognostic factors include younger patients, female gender, non oral squamous cell carcinoma, a long disease interval, no nodal metastasis at presentation and complete resection of the pulmonary metastasis.

Conflict of interest

None to declare.

References

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Appendix 1: Search strategy: MEDLINE

#1 Pulmonary [title/abstract] OR thoracic [title/abstract] OR lung [title/abstract]

#2 Metastasectomy [title/abstract] OR resection [title/abstract]

#3 Cancer [title/abstract] OR carcinoma [title/abstract] OR squamous cell carcinoma [title/abstract] OR malignancy [title/abstract] OR tumor [title/abstract] OR tumour [title/abstract]

#4 larynx [title/abstract] OR pharynx [title/abstract] OR oropharynx [title/abstract] OR hypopharynx [title/abstract] OR nasopharynx [title/abstract] OR oral [title/abstract] OR tonsillar [title/abstract] OR tongue [title/abstract]

#5 head AND neck [title/abstract]

#6 #4 OR #5

#7 #1 AND #2 AND #3 AND #6